

Identifying critically ill patients at high risk for developing acute renal failure: A pilot study

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Background. Acute renal failure (ARF) occurs commonly in the intensive care unit (ICU), but predicting which patients will develop ARF is difficult. We set out to determine which risk factors would predict the development of ARF in critically ill patients who are admitted to the ICU without ARF.

Methods. From August 2002 to April 2003, we enrolled medical-surgical ICU admissions into a cohort using a sampling tool based on their risk factor (RF) profile. The risk factors we identified were separated into 3 categories: chronic major, chronic minor, and acute RFs. Combinations of these RFs were used to create a sampling tool and identify patients to enroll into our cohort. Patients with end-stage renal disease and ARF upon admission to the ICU were excluded.

Results. We enrolled 194 patients over a 14-month period. The mean age of the cohort was 64.6 ± 14.7 years. The percentage of Caucasians, African Americans, and Hispanics was 40.7%, 50.5%, and 3.6%, respectively. In a univariate analysis of the entire cohort, increasing APACHE II quartile, increased A-a gradient, presence of systemic inflammatory response syndrome (SIRS), decreased levels of serum albumin, and presence of active cancer predicted ARF. In a multiple logistic regression analysis, decreased serum albumin (high levels of serum albumin were protective), increased A-a gradient, and cancer were associated with development of ARF (OR 2.17, 1.04, and 2.86, respectively).

Conclusion. Decreased levels of serum albumin concentration, increased A-a gradient, and presence of active cancer predict which patients who are admitted to the ICU will develop ARF.

Critically ill patients are at high risk for developing acute renal failure (ARF), which is associated with increased mortality [1]. Those critically ill patients with

ARF who require renal replacement therapy (RRT) have a mortality of 50% to 80% [1–3]. Despite the many advances in research techniques over the past 20 years, and the introduction of genomic and proteomic techniques, fundamental changes in the outcome of patients who develop ARF have not occurred [4]. The limited progress is related to many factors, including: (1) lack of a consensus definition for ARF; (2) lack of diagnostic tests that indicate the onset of ARF and renal injury; and (3) the absence of therapy for ARF aside from renal replacement therapy [5].

The considerable success of acute intervention in myocardial infarction is predicated on rapid, early recognition that allows swift therapeutic intervention. Similarly, it is likely that therapeutic agents will need to be initiated close to the time of renal insult in order for significant clinical benefit to be realized. Animal models of ARF using ischemic, toxic, and septic models have all suggested multiple therapeutic agents that appear to attenuate renal injury if administered before insult or shortly thereafter [6–12]. However, no randomized controlled studies in humans to date have shown benefit in treating established ARF [5, 13, 14].

The vast majority of ARF studies in humans (including the Anaritide and the Insulin Growth Factor-1 clinical trials) used increases in serum creatinine concentration (Scr) as the mainstay of determining which patients have ARF [13, 14]. Scr has significant limitations as a marker of renal injury. Scr is dissolved in extracellular water; when patients are volume expanded (e.g., resuscitation in patients with sepsis) decreases in glomerular filtration rate (GFR) are often not reflected by a commensurate increase in Scr. Because of these limitations, using increases in Scr as a marker of ARF prevents intervention at the onset of renal injury. In current clinical practice, the recognition of ARF often occurs many hours to days after the initial insult. An ideal kidney injury marker would have similar properties as the cardiac injury marker troponin. This injury marker would be characterized by specificity for kidney injury, and would become detectable in the

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blood or urine immediately after the onset of significant kidney injury. In order to delineate a biomarker that possesses the key characteristics mentioned above, samples must be acquired before the current clinical recognition of ARF occurs. Currently, ARF occurs in approximately 7.2% of hospital admissions [15]. If blood and urine were drawn daily (pre-kidney injury) in patients admitted to a hospital, only 7.2% of those samples would be relevant for kidney injury biomarker assessment. If, however, the selected cohort had a higher incidence of ARF, identified by predictive modeling, the yield for daily collection of blood and urine would be much higher. With this goal in mind, we set out to develop a risk factor model that could be used to identify the group of critically ill patients at highest risk for developing ARF.

Individual clinical variables that predict ARF have been described in subset groups of critically ill patients [6, 16]. The diversity of patients who become critically ill has created a large number of important predictors of ARF. These include but are not limited to: chronic kidney disease (CKD), pH <7.30, elevated severity of illness score (APACHE II, III or SAPS II), advanced age, history of congestive heart failure, elevated bilirubin, cirrhosis, cancer, mechanical ventilation, hypotension, oliguria, valvular surgery, use of intra-aortic balloon pump, increased body mass index, history of hypertension, and atherosclerotic cardiovascular disease (ASCVD) [1, 2, 4, 6, 16–22]. These studies were conducted in a retrospective fashion searching for the clinical and demographic predictors of ARF. We would like to be able to predict, on admission to the ICU, which patients during their stay in the ICU will experience ARF.

METHODS

According to the existing literature, some patients are at high risk for and others are at lower risk for developing ARF. We sampled our ICU admission population for patients that were at low and high risk for developing ARF. By using a screening tool to enter low- and high-risk patients into our cohort we hoped to eliminate patients who were at very low risk and those patients who are already in ARF because these types of patients are less informative.

We created a sampling tool based on the premise that comorbidities alone would not predict those patients at high risk for ARF. We speculated that the combination of well-known comorbidities associated with ARF [e.g., diabetes mellitus (DM), CKD, advanced age, and ASCVD] and acute risk factors (e.g., volume depletion, nephrotoxin exposure, sepsis) would prospectively predict those patients at high risk for ARF more frequently than either type of risk factor alone. Chronic and acute risk factors were determined by reviewing the ARF literature and by identifying comorbidities we felt to be

associated with ARF in our institution. The chronic risk factors we identified were: DM, CKD, ASCVD, advanced age (age >70 years), a history of hypertension (HTN), elevated serum bilirubin, cancer, morbid obesity (BMI >30 kg/m²), HIV infection, congestive heart failure, and history of cerebral vascular accident (CVA) [2, 4, 18, 21–23]. The acute risk factors were volume depletion, exposure to nephrotoxin, high-risk surgery, hypotension, and presence of systemic inflammatory response syndrome (SIRS) or sepsis.

We further classified chronic risk factors into 2 groups: major and minor. The major risk factors were: history or presence of DM, CKD, ASCVD, and age >70 years. The remaining chronic risk factors were designated minor risk factors. The definition of each risk factor is described in Table 1. The major, minor, and acute risk factors are summarized in Table 2. We decided to use a stratified risk factor system to determine our high-risk and low-risk groups. The high-risk group was defined as patients with 1 major risk factor plus 1 acute risk factor, 2 minor risk factors plus 1 acute risk factor, or 2 acute risk factors. Patients who were admitted to the ICU with preexisting ARF [defined by a rising Scr (increase of 50% from baseline) or a urine output less than 0.5 mL/kg/hr for the 12–48 hours before enrollment] were excluded. The low-risk group was defined as patients with 1 major or 1 acute risk factor, but not both. The criteria for both groups are shown in Table 3.

This study was conducted from August 2002 to April 2003 in the hospital ICU. The George Washington University Hospital ICU is a 48-bed combined medical-surgical ICU that admits all critically ill adults, except those with major thermal injuries. A waiver of informed consent was obtained from the Institutional Review Board (IRB) because the study involved chart review only. In addition, because the study spanned the initiation of the HIPAA law, we obtained a HIPAA waiver from the George Washington University Committee on Human Research and the privacy officer of the hospital.

All patients in the study were enrolled within 36 hours of admission to the ICU. Each day, all new admissions were evaluated for entry into the high-risk group. Each day admissions were evaluated in the same order. Once a patient was identified, he or she was enrolled in the study. Patients were enrolled as pairs. After the first patient was identified, a patient for the low-risk group was also identified and enrolled. If a low-risk patient could not be identified, a high-risk patient was not enrolled in the study on that day. On any given day, once a pair of patients were identified and enrolled, any other newly admitted patients that met high-risk criteria could also be enrolled on that day. Once a subject was enrolled, demographic data, clinical data, and relevant past medical history were obtained, and these data were used to calculate an admission APACHE II score. A gradient was

Table 1. Definitions of risk factors

Risk factor	Definition
Chronic kidney disease (CKD)	Creatinine >2.0 mg/dL in men, or >1.8 mg/dL in women
Advanced age	>70 years
Atherosclerotic cardiovascular disease (ASCVD)	History of angina pectoris, CAD, myocardial infarction, or peripheral vascular disease
Diabetes mellitus (DM)	History of diabetes mellitus
Congestive heart failure (CHF)	New York Heart Association Grade III or IV heart failure
History of hypertension (HTN)	History of hypertension or patients receiving chronic hypertensive medications
Hyperbilirubinemia	Serum total bilirubin >2.0 mg/dL
Morbid obesity	BMI >30.0 kg/m ²
Cancer	Active cancer (patients not in remission and without surgical cure)
HIV infection	History of testing positive for HIV antibodies
History of cerebrovascular accident (CVA)	History of any type of CVA
SIRS/Sepsis	SIRS: 2 of these findings: respiratory rate >20/min, pulse >90/min, temperature >38°C or <36°C, white blood cell count >12,000/mL or <4000/mL; or sepsis: SIRS with suspected or proven microbial origin
Hypotension	MAP <70 mm Hg or any vasopressor except dopamine dosed at less than 5.0 µg/kg/minute
Volume depletion	Central venous pressure (CVP) <6 cm of H ₂ O or pulmonary capillary wedge pressure (PCWP) <8 cm of H ₂ O
High-risk surgery	Cardiac surgery (valvular or coronary artery bypass grafting), aortic surgery, hepatobiliary surgery (excluding cholecystectomy)
Nephrotoxin exposure	Amphotericin B, aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAIDs), excluding aspirin, radiocontrast given within 24 hours

calculated using the sea level standard formula $[(713 \times (\text{FIO}_2) - (\text{PCO}_2/0.8)) - \text{PaO}_2]$. In addition, all major, minor, and acute risk factors present at time of enrollment were recorded. Subjects were followed throughout their ICU stay; the primary end point of the study was the development of ARF in the ICU. The secondary end point was the need for RRT. Because there was no validated consensus clinical definition of ARF at the time this study was initiated, we used the definition of ARF outlined here: >75% increase in serum creatinine if baseline creatinine ≤ 2.0 mg/dL, or >50% increase in serum creatinine if baseline creatinine >2.0 mg/dL (a serum creatinine of 1.8 mg/dL was used if the patient was female).

Statistics

Proportions of patients with certain characteristics were compared using the chi-square test. We assessed the distribution of variables. Variables with normal distribution were compared using two-tailed unpaired *t* tests, while data that did not conform to a normal distribution were compared using the Mann-Whitney rank sum test. Major risk factors, minor risk factors, acute risk factors, APACHE II score, and other clinically applicable variables were entered into a univariate logistic regression with ARF as the dependent variable. Once univariate predictors of ARF were identified, these variables were then entered into a multivariate regression model with ARF as the dependent variable. Age was placed into the equations as a continuous variable, and as age decile. Similarly, APACHE II score was entered into equations as a continuous variable and as APACHE II quartile. Unless otherwise specified, all means are reported as \pm SD. All

Table 2. Summary of the chronic and acute risk factors

Chronic major risk factors	Advanced age, DM, ASCVD, or CKD
Chronic minor risk factors	HTN, morbid obesity, elevated bilirubin, CVA, HIV, or cancer
Acute risk factors	Hypovolemia, hypotension, high-risk surgery, nephrotoxin exposure, SIRS, or sepsis

Table 3. Definition of groups

High-risk group	Low-risk group
1 acute risk factor + 1 major risk factor OR	1 major risk factor or 1 acute risk factor (BUT NOT BOTH)
1 acute risk factor + 2 minor risk factors OR	Multiple major risk factors without acute risk factors
2 acute risk factors	Multiple major and minor risk factors without acute risk factors

statistics were performed with SPSS 11.0 (SPSS, Chicago, IL, USA).

RESULTS

We enrolled a total of 194 patients over a 14-month period. The mean age of the cohort was 64.6 ± 14.7 years. The percentage of Caucasians, African Americans, and Hispanics was 40.7%, 50.5%, and 3.6%, respectively. The percentage of men was 53.6%. The prevalence of diabetes, ASCVD, and CKD was 36.6%, 30.4%, and 18%, respectively. The mean body mass index (BMI) was 28.3 ± 10.4 kg/m² and the mean serum albumin was 3.00 ± 0.79 g/dL. The mean APACHE II score was 12.5 ± 5.6 . The incidence of ARF based on our definition was 18.0% (35 cases). Of the 35 patients that developed ARF, 13

Table 4. Demographic characteristics of the patients

Variable	ALL	HRG	LRG	P value
Age years	64.6 ± 14.7	66.4 ± 14.6	62.8 ± 15.7	0.12
Race (AA)	50.5%	56.7%	40.8%	0.24
Gender male	53.6%	60.3%	57.9%	NS
APACHE II	12.5 ± 5.6	13.5 ± 5.5	11.0 ± 6.1	<0.001 ^a
APACHE II range	2–35	3–31	2–35	
Incidence of ARF	18.0%	27.1%	3.9%	0.001 ^a
Need for RRT	6.7%	10.2%	1.3%	0.025 ^a

Abbreviations are: HRG, high-risk group; LRG, low-risk group; ARF, acute renal failure, RRT, renal replacement therapy.

^a $P \leq 0.05$.

Table 5. Univariate predictors of ARF

	OR	95% CI	P value
Age decile	0.93	0.74–1.18	0.57
Chronic kidney disease	1.77	0.74–4.2	0.20
Diabetes mellitus	0.88	0.41–1.91	0.75
ASCVD	0.90	0.40–2.01	0.79
Hypertension	0.80	0.37–1.71	0.56
Cancer	3.75	1.68–8.4	0.001 ^a
Morbid obesity	2.1	0.79–5.50	0.14
Congestive heart failure	1.85	0.74–4.58	0.19
Cerebrovascular accident	0.001	0.00–inf	0.96
Elevated serum bilirubin	3.6	0.78–17.0	0.10
SIRS	3.11	1.46–6.65	0.003 ^a
High-risk surgery	1.51	0.68–3.37	0.31
Nephrotoxic exposure	0.001	0.00–inf	0.96
Hypotension	0.85	0.35–2.12	0.73
pH	0.18	0.005–6.4	0.35
Serum albumin	0.40	0.24–0.69	<0.001 ^a
A-a gradient	1.044	1.015–1.074	0.003 ^a
FIO ₂	1.01	0.99–1.030	0.07
APACHE II quartile	1.57	1.11–2.24	0.012 ^a

^a P value ≤ 0.05 .

(37.1%) required RRT. None of the patients in our cohort who developed ARF died before requiring RRT.

One hundred and eighteen patients were enrolled in the high-risk group (HRG), and 76 were in the low-risk group (LRG). The demographic characteristics of the 2 groups were well matched (Table 4). The mean age of the HRG and the LRG was 66.4 ± 14.6 and 62.8 ± 15.7 years, respectively ($P = 0.12$). There were 67 (56.7%) African Americans in the HRG and 31 (40.8%) African Americans in the LRG. The percentage of men in the HRG and the LRG was 60.3% and 57.9%, respectively ($P = NS$). The mean APACHE II score for the HRG was 13.5 ± 5.5 while the mean APACHE II score for the LRG was 11.0 ± 6.1 ($P < 0.001$). The incidence of ARF in the HRG was 27.1% and 3.9% in the LRG ($P = 0.001$) (Table 4); 10.2% of patients in the HRG and 1.3% of the LRG patients required RRT ($P = 0.025$).

Clinical and demographic variables were assessed as univariate predictors of ARF. A complete list of the univariate relative risks and confidence intervals are provided in Table 5. Age (years), age decile, presence of diabetes, ASCVD, CKD, HTN, BMI, history of CVA, serum bilirubin, history of CHF, presence of hypotension, high-risk surgery, presence of nephrotoxin, and pH did

Table 6. Biochemical + preexisting condition models

Biochemical predictors	RR	Confidence Intervals	P value
Serum albumin	0.45	0.24–0.85	0.013
A-a gradient	1.040	1.010–1.071	0.009

Preexisting condition predictors	RR	Confidence Intervals	P value
SIRS	2.81	1.28–6.14	0.01
Active cancer	3.38	1.48–7.73	0.004

Table 7. Multivariate analysis

	RR	Confidence Intervals	P value
SIRS	1.224	0.45–3.33	0.69
Active cancer	2.814	1.01–7.85	0.048
Serum albumin	0.479	0.25–0.92	0.027
A-a gradient	1.039	1.01–1.07	0.015

Table 8. Multivariate analysis

	RR	Confidence Intervals	P value
Active cancer	2.86	1.03–7.97	0.044
Serum albumin	0.46	0.25–0.86	0.016
A-a gradient	1.04	1.01–1.07	0.013

not predict the development of ARF. Presence of SIRS and history of cancer predicted ARF, with a relative risk of 3.11 (95% CI 1.46–6.65, $P = 0.003$) and 3.8 (95% CI 1.68–8.38, $P = 0.001$), respectively. For each 10 mm Hg increase in A-a gradient there was a 4.4% increased relative risk of developing ARF (RR 1.044, 95% CI 1.015–1.074, $P = 0.003$). Increased serum albumin concentration was associated with a relative risk of 0.4 of developing ARF (95% CI 0.24–0.69, $P < 0.001$). In addition, APACHE II quartile predicted the development of ARF with a relative risk of 1.6 (95% CI 1.1–2.24, $P = 0.012$).

Multivariate regression models built from the univariate predictors of ARF are summarized in Tables 6, 7, and 8. We developed 4 multivariate models based on the 5 univariate parameters that predicted ARF, a biochemical model including serum albumin and A-a gradient, and a preexisting condition model including history of cancer and presence of SIRS (Table 6). When APACHE II quartile was added to either of the biochemical or preexisting condition models, APACHE II quartile did not predict ARF (data not shown). In Table 7, biochemical predictors and preexisting conditions are combined into a multivariate model. In this model, history of cancer, serum albumin, and A-a gradient still predict ARF, whereas presence of SIRS does not predict ARF. In Table 8, the 3 remaining predictors of ARF (presence of serum albumin, history of cancer, and A-a gradient) are entered into a model, and all 3 of these variables predict the development of ARF.

DISCUSSION

In this pilot study of medical and surgical critically ill patients we have been able to identify predictors of ARF. In our pilot study, low serum albumin, increased A-a gradient, and history of cancer were predictors of ARF upon admission to the ICU. In addition, we found that combinations of known risk factors were associated with a more precise detection of ARF compared to solitary risk factors. If these predictors of ARF can be used to create a predictive model two major advances might be realized. One, modeling would allow efficient collection of serum and urine specimens for biomarker analysis. Two, given the poor tests in current use for diagnosis of ARF, a preventive therapeutic trial could use modeling to target patients at high risk for developing ARF. Instead of waiting for ARF to develop, patients who are determined to be at high risk for ARF could start to receive preventive/therapeutic agents upon ICU admission based on their ARF risk profile. For example, if the general ICU incidence of ARF were 10%, and a preventive drug (e.g., N-acetyl cysteine) were given to all ICU patients upon admission, for every 10 patients, 9 would be unnecessarily exposed to the intervention, while only 1 patient would potentially gain benefit. If this type of model can be enriched to 35% to 40% yield, the number of patients needed to treat at highest risk for ARF would decrease.

Decreased levels of serum albumin have been shown to be a predictor of mortality in patients with end-stage kidney disease and in patients with ARF [24–27]. Coritsidis et al have successfully used a “bedside formula,” which utilizes the serum albumin to predict which patients will develop ARF [28]. In their model, the “bedside formula” predicted ARF better than APACHE scoring. In an historic cohort, Ward showed that low serum albumin predicted which patients with rhabdomyolysis would develop ARF [29]. In patients who are critically ill, decreased levels of serum albumin have often been ascribed to poor nutritional status. However, serum albumin can also fall significantly in response to inflammation and capillary leak [30]. In our cohort of patients, it is impossible to determine if the contribution of serum albumin to the development of ARF is more related to nutritional status or with degrees of inflammation. Increased serum concentrations of proinflammatory markers have been shown to predict death in a variety of patient populations, and poor nutritional status has long been known to be associated with increased mortality [31–33]. Malnutrition, as measured by the subjective global nutritional assessment (SGA), is associated with a poor clinical outcome in patients with ARF [34]. Serum albumin is a part of the SGA, but it is only one part of the biochemical component of the SGA. If decreased levels of serum albumin are validated in large cohorts of critically ill patients as a predictor of ARF, the additional assessment of other nu-

tritional and inflammatory parameters (e.g., prealbumin, C-reactive protein, serum concentration of proinflammatory cytokines, etc.) would be useful in discriminating why serum albumin predicts ARF. In our cohort, SIRS predicted ARF as a univariate parameter, but did not predict ARF in the multivariate analysis. Because serum albumin concentrations often fall in the face of inflammation, it is likely that in our cohort SIRS and decreased serum albumin are colinear.

We also demonstrated that increased A-a gradient was predictive of ARF. In a mixed med-surgical population of critically ill patients, de Mendonca et al demonstrated that respiratory failure was a predictor of the development of ARF as measured by renal sequential organ failure assessment [2]. In our study, we did not specifically code for respiratory failure because the decision about when to intubate a patient can be quite subjective (e.g., airway protection, change in mental status, respiratory distress, etc.).

The presence of active cancer was a strong determinant of ARF in our cohort. Patients who have active cancer are often exposed to a variety of clinical conditions known to cause ARF. Patients receiving chemotherapy are often treated with nephrotoxic chemotherapeutic agents [35, 36]. Cancer patients are also at risk for tumor lysis syndrome, volume depletion, direct toxicity from the neoplastic disease (e.g., multiple myeloma), and obstructive renal disease due to mass occupying lesions [37–39]. In addition, renal tubular cell recovery has been shown to be impaired in animals that have received bone marrow suppression [40, 41]. When patients become critically ill, they are at a disadvantage due to their cancer burden and concomitant immunosuppression. This background, in combination with the multiple types of renal injury that may have preceded or are concurrent with critical illness, makes cancer patients particularly vulnerable to the development of ARF [42]. In large cohorts of critically ill patients, active cancer may be an underappreciated risk factor.

Other investigators have assessed which risk factors are associated with the development of ARF in subset groups of critically ill patients (postcardiac surgery patients, trauma patients, and patients with sepsis) [16, 21, 24, 43, 44]. However, there is only one study of which we are aware that evaluated critically ill patients taken as a whole. De Mendonca et al evaluated a cohort of 1411 critically ill patients and used their renal sequential organ failure assessment (SOFA) to evaluate the development of ARF [2]. Patients who achieved a renal SOFA score of 3 (serum creatinine >3.0 mg/dL or urine output <500 mL/day) were considered to have developed ARF. The most important risk factors for the development of ARF present on admission were acute circulatory or respiratory failure, age greater than 65 years, presence of

infection, past history of chronic heart failure (CHF), lymphoma, leukemia, or cirrhosis. The population de Mendonca et al [2] studied is the most similar to our population of critically ill patients. As in their study, we identified cancer and acute respiratory disease as significant risk factors for the development of ARF. We speculate that active cancer and respiratory disease will remain important predictors of ARF in future validated prediction models of ARF.

Unlike de Mendonca's study [2], we excluded patients who were admitted to the ICU already suffering from ARF. There are limited epidemiologic data available comparing patients who develop ARF after ICU admission versus those patients who have ARF on admission to the ICU. Guerin et al found patients who arrived in the ICU with ARF had a lower mortality (61%) than patients who develop ARF later in their ICU stay (71–81%) [45]. Further evaluation of these subgroups is warranted.

Our study has several limitations that may limit the generalizability of our high-risk profile. First, the sample size of our population was relatively small. Second, we chose a high-risk group and a low-risk group in order to generate our cohort, but all of the admissions to the ICU were not captured. In order to know how well the high-risk group model performs, all ICU admissions should be captured in order to determine the sensitivity, specificity, negative, and positive predictive value of this "test." Third, the etiology of ARF was not determined. Fourth, our definition of ARF was arbitrary. Currently, there is no validated consensus definition for ARF, and we anxiously await the validation of the RIFLE criteria (Acute Dialysis Quality Initiative, www.adqi.net).

CONCLUSION

Risk factor profiling is a useful technique in identifying those critically ill patients at high risk for developing ARF. Risk factor profiling may be an important element in the design of preventive clinical trials in patients at risk for developing ARF. Risk factor profiling is not a surrogate marker of severity of critical illness. Decreased levels of serum albumin, elevated A-a gradient, and active cancer appear to be strong determinants of the development of ARF in patients who are critically ill. We are currently conducting a prospective observational study of all ICU admissions in order to validate these predictors of ARF. We plan to develop a model that can accurately predict which critically ill patients are at highest risk for developing ARF.

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